

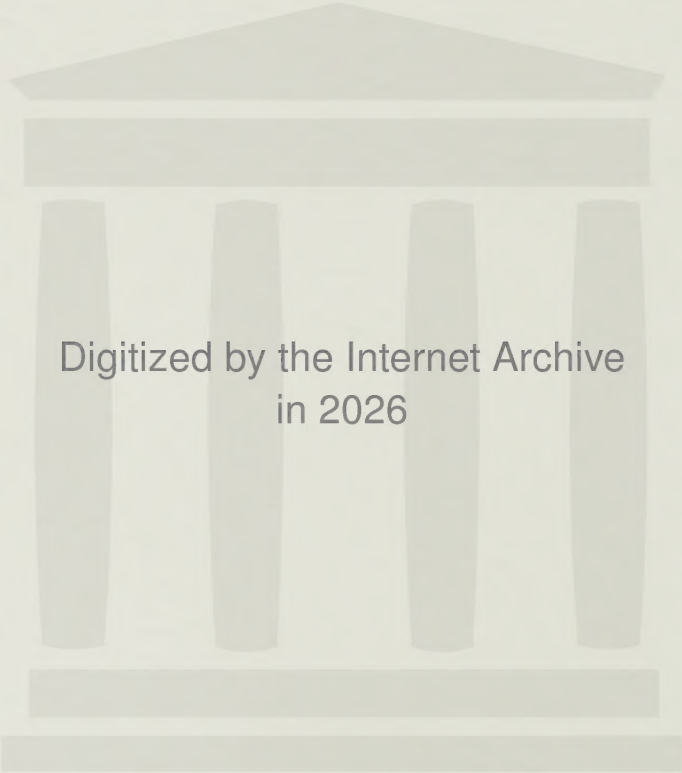
Aus dem Zentrum für Innere Medizin
des Bereichs Humanmedizin
der Justus Liebig-Universität Gießen
Geschäftsführender Direktor: Prof. Dr. H. G. Lasch

PHARMACOKINETICS OF PINDOLOL IN MAN

Inaugural-Dissertation
zur
Erlangung des Doktorgrades
des Bereichs Humanmedizin
der
Justus Liebig-Universität Gießen

vorgelegt von
Werner Herold
aus Homberg

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Pindolol (Visken^R), DL-4-(2-hydroxy-3-isopropylaminopropoxy)-indole, is a potent β -adrenoceptor blocking agent with a negligible effect on basal cardiovascular function in the normal (LEVY, 1971) differing from propranolol in being 5 to 10 times as potent on a weight basis and in possessing intrinsic agonist activity (BARRETT and CARTER, 1970).

The structural formula (Fig. 1) is related to other β -blocking compounds all showing an isopropylamine residue at the side chain. Nevertheless, these drugs are different in the intensity of action on several β -receptor carrying organs. The pharmacokinetic behavior in man is also fundamentally different and not predictable from the chemical structure (FITZGERALD and SCALES, 1968; SHAND et al., 1970; JOHNSON et al., 1971; ABLAD et al., 1972; GEORGE et al., 1972; BODEM and CHIDSEY, 1973). In order to establish rational dosage schedules, basic pharmacokinetic parameters of a drug should be available. Although the various pharmacological activities of pindolol were investigated intensively (SAAMELI, 1967; HILL and TURNER, 1967, 1969; GIUDICELLI et al., 1969; LUBAWSKI and WALE, 1969; BARRETT and CARTER, 1970; LEVY, 1971), there is little information on the pharmacokinetic behavior of this compound in man. Some preliminary data (HICKS et al., 1972) after the intravenous administration of 0.6 mg of pindolol to 4 subjects indicate a mean plasma half-life time of 3.4 hours. The plasma concentrations, however, showed considerable standard deviations. This is not a surprising fact as these plasma levels were all below 4 ng/ml which is near the lower limit of detection of the method used in the investigation (PACHA, 1969).

This study describes the absorption, distribution, and excretion pattern of pindolol after oral and intravenous administration.

Materials and methods

Estimation of pindolol in plasma and urine

Pindolol concentration was measured using a slightly modified method described by PACHA (1969).

A. Plasma: 5 ml of plasma from blood containing 2 drops of heparin (Liquemin^R) were made alkaline by adding 1 ml of 1 N sodium hydroxyde and extracted with 12 ml of diethylether by shaking for 10 minutes by an automatic shaker. Of a 10 ml aliquot of the organic layer the compound was reextracted into 2 ml of 0.1 N hydrochloric acid. 1.5 ml of the acidic layer was reacted with 0.5 mg of O-phthalaldehyde by heating in a water bath at 50⁰ C for 30 minutes. The solution was then stabilized by adding 0.5 ml of ascorbic acid and examined in an Aminco Bowman spectrophotofluorometer at excitation and emission maxima of 390 and 440 nm, respectively.

B. Urine: 5 ml of urine were diluted with 5 ml of distilled water. 2 ml of 10% zinc sulphate solution and 1 ml of 1 N sodium hydroxyde were added and the precipitate formed separated by short centrifugation. The solution was further alkalized with 1 ml of 1 N sodium hydroxyde and the drug extracted into 10 ml of 1.5% benzene-isoamyl alcohol. After reextraction into 2 ml of 0.1 N hydrochloric acid the procedure was identical with that used for plasma.

Clinical Studies

17 consenting volunteers (9 male and 8 female) participated in these studies, all being between 19 and 30 years of age, body weight varying between 50 and 80 kg. The subjects were considered healthy as judged by history, physical examination and laboratory tests including creatinin clearance.

Oral administration: 12 subjects fasted overnight and received pindolol in a dose of 5 mg as a tablet. Blood samples were obtained before and at the following times after the administration: 0.5 - 1 - 2 - 3 - 4 - 6 - 8 - 12 - 24 hours. Blood was centrifuged immediately and the plasma stored at 4° C no longer than one day before the analysis. Urine was collected in fractions over the periods 0 - 4, 4 - 8, 8 - 12, 12 - 24 hours.

Intravenous administration: 5 mg of the drug were infused in 50 ml saline at a constant flow rate over 3 hours. The fraction of drug remaining in the ampules and in the infusion system after the infusion period was washed out and the amount determined for subtracting it from the nominal dose of the ampules. Blood samples were obtained usually 15, 90, 165, and 180 minutes during the infusion period and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours following the end of the infusion. Urine collection periods were during infusion (3 hours) and 0 - 4, 4 - 8, 8 - 12, 12 - 24 hours following the end of the infusion.

Blood pressure and heart rate were recorded in sitting position at every time of taking blood samples.

Protein binding

Protein binding was studied by means of gel chromatography on Sephadex G 25 according to a procedure described by KRIEGLSTEIN & KUSCHINSKY (1968) using a 4% human serum albumin solution. Drug concentrations were 60 ng/ml of protein solution representing the upper range of plasma levels achieved by oral dosing.

Calculations were performed on a desk computer Olivetti Programma P 602 and a Wang 300 computer, respectively.

R e s u l t s

Clinical

No change in blood pressure at rest was observed during all studies. Resting heart rate in some cases declined slightly but not to a significant degree. Adverse effects were not registered, with the exception of moderate headaches in two cases.

Plasma level

Plasma levels of all investigations are given in tables 1 and 2. The time course of the mean plasma levels after oral administration is shown in figure 2 ($\bar{x} \pm S_{\bar{x}}$). Most of the individual plasma level time curves are compatible with a one-compartment model and described by the bateman function. There is a rapid increase of concentration during the first hour with maximum plasma levels determined graphically at about 80 minutes

followed by a linear decline in the semilogarithmic plot between 3 hours and the end of the experiment. The correlation coefficients of the individual regression lines in the linear parts of the slopes vary between 0.92 and 0.99. Mean maximum plasma levels are 33.1 ± 5.2 ng/ml with a great individual variation between 19 and 81 ng/ml plasma which means a 4-fold difference in the plasma level response in the different subjects.

Following the intravenous infusion of pindolol, the plasma levels fell strictly linear with time on a semilogarithmic plot after the end of the infusion period (figure 3) in 4 out of 5 subjects tested. This has been proved by calculating the regression lines twice, from the final point of estimation of plasma level back to 2 hours after the end of the infusion period, and from the final point back to the very end of the infusion period. This procedure demonstrated that the correlation coefficients did not get worse when the first 2 hours of the declining slope after the end of the infusion were included, but even improved in 3 curves. In one subject (C) a biphasic decline of the plasma level curve was observed with a terminal slope beginning after 60 minutes. This subject was identical with that one showing a surprisingly high urinary excretion of 76.8% after 24 hours as mentioned below.

From these findings it can be concluded that at least after intravenous infusion of 5 mg over 3 hours as used in this study there usually is a monoexponential decline of the plasma level time curve. It, therefore, seems allowable for this study to calculate the pharmacokinetic data of pindolol in the assumption of an open one-compartment model. After constant

infusion periods a variation of peak plasma levels was also observed with maximum concentrations in a range between 17 and 59 ng/ml.

Urinary excretion

The time course of the cumulative excretion in urine after oral and intravenous administration is shown in figure 4. The curves rise rapidly during the first 12 hours while for the 12 - 24 hours period the slope is rather flat. It seems likely, therefore, that the amount of drug excreted in the urine after 24 hours does not play an important role for the total urinary excretion. The mean value for the cumulative excretion at 24 hours after oral administration is $32.3 \pm 3.0\%$, after intravenous infusion $38.9 \pm 0.9\%$. The data after the infusion test of one subject (C) are not included in this calculation as he is the only one out of 17 who shows an enormously high total excretion of 76.8% even after 24 hours. As the excretion rates ($\mu\text{g} \times \text{h}^{-1}$) for the individual subjects plotted on a semilogarithmic scale decline linearly with time (Fig. 5), the half life time of urinary excretion can be calculated for both routes of administration. It is 5.41 ± 0.68 hours after oral and 3.68 ± 0.37 hours after intravenous administration of pindolol. Compared with the plasma half life times of the i.v. administered compound (3.13 ± 0.52), no significance could be evaluated while there is a significant difference after oral ingestion ($p < 0.05$) where plasma half life time is 3.65 ± 0.24 hours (Table 3).

Protein binding

The amount of protein bound pindolol in serum determined by column chromatography on Sephadex G 25 was 57.2% taking the average of three experiments.

Pharmacokinetic data

The pharmacokinetic parameters of pindolol that can be evaluated from an analysis of plasma levels and urinary excretion are listed in tables 3 and 4. The time course of the plasma levels after intravenous infusion suggest that our data are compatible with the linear open one-compartment system. Accordingly, the time course of plasma levels after oral administration can be described by the Bateman function.

The plasma elimination rate constant k_2 is determined by calculating the regression lines of the linear declining slope for both the oral and the intravenous form of administration and dividing the calculated slopes by $\log e$. The mean k_2 -value is $-0.20 \pm 0.01 \text{ h}^{-1}$ after oral and $-0.25 \pm 0.04 \text{ h}^{-1}$ after intravenous application (Tables 3, 4). The difference in the two slopes is not significant when evaluated by the students t-test.

According to

$$t_{0.5} = \frac{\ln 2}{k_2}$$

the plasma half lives were 3.65 ± 0.24 hours (oral) and 3.13 ± 0.55 hours (i.v.) respectively.

The fictive initial concentration C_0 is in the case of oral administration calculated by extrapolating the regression lines to zero time. It is $33.08 \pm 5.24 \text{ ng/ml}$ with the 4-fold variation

mentioned above. After the intravenous infusion C_0 is the initial concentration which would have been obtained if the total dose were administered as bolus injection. C_0 is calculated by $C_0 = F_0^\infty \times k_2$. F_0^∞ is the total area below the serum curves determined by summing up the areas according to $F_0^\infty = F_0^n + F_n^\infty$, where F_0^n is $= \frac{y_1 - y_2}{2} \times t$ and $F_n^\infty = \frac{C_n}{k_2} \cdot C_0$ (i.v.) is 41.18 ± 9.55 ng/ml.

The cumulative urinary excretion at $t = \infty$ was calculated approximating the cumulative excretion by an exponential equation of the form $E_U^t = E_U^\infty (1 - e^{-k_2 \cdot t})$ (Table 3, 4). Mean values for the cumulative urinary excretion at $t = \infty$ were $39.18 \pm 0.91\%$ after intravenous and $36.14 \pm 4.37\%$ after oral administration respectively.

The absorption rate is determined by the following method: The cumulative urinary excretion values of pindolol after oral and intravenous administrations are compared. This procedure gives exact data (NOESCH, 1973) on the absorption rate provided that the excretion is calculated at $t = \infty$ and the model is linear. The method may be used, too, as is the experience in this laboratory, when oral and i.v. studies are performed on different subjects. The absorption rate of pindolol calculated by using these data was 92%.

Another method for determining absorption rates, based on the comparison of the total areas below the plasma level curves ($C \times t$) after oral and intravenous application of a drug, might be applicable also to interindividual trials, as suggested by DENGLE (1970, 1973), for sparteine and digitalis glycosides. The total areas below the plasma level curves corrected by the

slightly different doses were in the case of oral administration $239.2 \pm 37.2 \text{ ng} \times \text{h} \times \text{ml}^{-1}$, and of intravenous administration $195.6 \pm 29.6 \text{ ng} \times \text{h} \times \text{ml}^{-1}$. This difference is not significant ($t = 0.71$; $p > 0.05$). If a nearly complete absorption of 92% can be assumed, as shown when the cumulative urinary excretion after oral and intravenous administration is compared, this assumption is supported by the finding of identical total areas below the plasma level curves.

The distribution volume V_D is calculated by the equation

$$V_D = \frac{D \cdot f}{k_2 \cdot F_0^\infty}$$

where D is the dose administered intravenously and f is the absorption quotient which after i.v. application is 1.0 and in the case of orally administered pindolol 0.92 (92% absorption). The mean volume of distribution calculated for both applications is $136 \pm 32 \text{ l}$ and $142 \pm 17 \text{ l}$ respectively. Corrected by the body weight of the subjects, a relative distribution volume of $2.0 \pm 0.48 \text{ l}$ and $2.1 \pm 0.24 \text{ l}$ could be evaluated.

The invasion^{rate} constant k_1 after the oral administration of pindolol has been evaluated by two methods:

1. The SIGMA-MINUS method is based on plotting the "residuals" between the extrapolated regression line and the really measured plasma levels at the different times of the invasion period on a semilogarithmic scale and calculating the invasion rate constant according to $k_1 = \text{slope} / \log e^{(21)}$.

2. According to DILLER (1961) the rate constant of invasion is described by

$$k_1 = k_2 \cdot \frac{C_0}{C_0 - a}$$

where C_0 is the fictive initial plasma concentration obtained by extrapolating the regression line to $t = 0$, and "a" is calculated as

$$a = F_0^\infty \times k_2$$

The mean invasion constant calculated by method I is $1.23 \pm 0.14 \text{ h}^{-1}$, calculated by method II $2.36 \pm 0.52 \text{ h}^{-1}$. Using the k_1 -values of the individual curves, the invasion half life time is calculated to be $0.63 \pm 0.07 \text{ h}$ and $0.41 \pm 0.06 \text{ h}$ respectively.

The time of peak plasma level after oral administration of pindolol is calculated by

$$t_{\max} = \frac{1}{k_1 - k_2} \cdot \ln \frac{k_1}{k_2}$$

It is found to be 1.42 ± 0.17 when the DILLER method is applied and $1.88 \pm 0.15 \text{ h}$ when the SIGMA-MINUS method is applied. Using the k_1 -values obtained by the DILLER method, the calculated $t_{\max}$ fits better to the $t_{\max}$ determined graphically in the individual plasma level time curves, so that the $t_{\max}$ of 1.42 h is considered to represent the real situation better.

To determine the renal clearance, a procedure by WAGNER (1969) is used, defining renal clearance as the relation of the amount of drug excreted in urine at $t = n$ ($A_u; n$) to the area below the plasma level time course at time n (F_0^n), obtained by the

DOST' squares,

$$Cl_{ren} = \frac{A_u; n}{F_o^n}$$

Renal clearance by this method was found to be $163.2 \pm 20 \text{ ml} \cdot \text{min}^{-1}$ ($\bar{x} \pm S_{\bar{x}}$) for the oral administration and $216.1 \pm 48.4 \text{ ml} \cdot \text{min}^{-1}$ for the intravenous administration. Total clearance calculated by $Cl_{tot} = k_2 \cdot V$ was $425.8 \pm 51.5 \text{ ml} \cdot \text{min}^{-1}$ and $483.3 \pm 79.6 \text{ ml} \cdot \text{min}^{-1}$ respectively. The differences in the clearances after oral and intravenous administration are not significant.

D i s c u s s i o n

The pharmacokinetic data of pindolol presented in this study after oral and intravenous administration may be interpreted in terms of an open one-compartment model. Though appreciating the criticism by GIBALDI et al. (19) that the open two-compartment model in most instances is the more appropriate one, we felt justified to evaluate our data in the proposed way as no major changes in the final pharmacological parameters became evident. For safety reasons, the rapid injection technique of high enough doses to produce reliably measurable plasma levels was discarded and the technique of a slow infusion over 3 hours was preferred to prevent adverse reactions.

After oral administration of the drug absorption occurs rapidly as shown by $t_{max} = 1.42 \text{ h}$. Nearly identical times of maximum plasma levels have been shown with other beta-receptor blocking agents, propranolol (PATERSON et al., 1970), practolol (BODEM

and CHIDSEY, 1973), and alprenolol (ABLAD et al., 1972), estimated by evaluating graphically the plasma level time curves presented in these studies.

Of special interest is the fact that after both the oral and intravenous administration maximum plasma concentrations of pindolol exhibit a 4-fold variation. As this variation is also found after intravenous application, it cannot be explained by differences in the absorption rates between various subjects. Similar results are reported with propranolol (SHAND et al., 1970) supporting the thesis that the plasma level of the drug is better correlated to its effect than the dose (KOCH-WESER, 1972). It could be demonstrated in another study, however, that despite a good correlation between the logarithm of the plasma concentration of pindolol and its beta-blocking activity for the individual subject, there are remarkable differences in the intersubject relation of beta-blocking effect to the actual plasma level of pindolol (GUGLER et al., 1973).

The plasma half life time considered to be the most important pharmacokinetic parameter of a drug was found to be 3.65 ± 0.24 hours after orally and 3.13 ± 0.55 hours after intravenously administered pindolol, this difference being not significant. For propranolol similar differences in half life time between oral and intravenous administration are described, corresponding values being 3.0 ± 0.79 hours and 2.34 ± 0.22 hours, respectively (SHAND et al. 1970).

Pindolol plasma level of 10 ng/ml has been evaluated as the minimum concentration producing a beta-receptor blocking effect

(GUGLER et al., 1973) though recent results give evidence that the effect of pindolol lasts longer than 24 hours after one oral dose (OLSSON and VARNAUSKAS, 1973). As shown in figure 2, with an oral dose of 5 mg a plasma level of 10 ng/ml is usually found even 30 minutes after ingestion and is exceeded over a period of 6 - 8 hours. The shorter half life time of propranolol (2.3 - 3.0 hours) necessitates shorter dose intervals or higher single doses. Alprenolol is reported to have a plasma half life time of about 3.5 hours (ABLAD et al., 1972) whereas practolol is the only compound of this group of drugs presently known having a long plasma half life time^{of} about 13 hours (BODEM and CHIDSEY, 1973). The half life time of urinary excretion of pindolol was 3.68 ± 0.37 hours (i.v.) and 5.41 ± 0.68 hours (oral), only the latter being significantly different from the corresponding plasma half life time.

The absorption rate of pindolol of 92% corresponds to that found with practolol (BODEM and CHIDSEY, 1973) and propranolol (PATERSON et al., 1970). Cumulative excretion rates of 40% at $t = \infty$ indicate that the drug is extensively metabolized. While propranolol is metabolized even to a higher degree, practolol is not metabolized at all in man. These compounds are completely identical concerning the side chain which is considered to be responsible for the beta-receptor blocking activity of this group of drugs. It seems likely, therefore, that the side chain cannot be of any influence on the degree of metabolization of beta-blocking agents, whereas the nucleus mainly determines the rate of biological degradation.

If elimination routes other than renal are excluded, the difference between total and renal clearance of a drug is supposed to

be the metabolic clearance giving evidence about the degree of metabolization. In the case of practolol total clearance and renal clearance are identical, confirming the finding that the compound is not metabolized. The total clearance of pindolol, however, is $483 \text{ ml} \times \text{min}^{-1}$ and the renal clearance is $216 \text{ ml} \times \text{min}^{-1}$, indicating a high metabolic clearance of $267 \text{ ml} \times \text{min}^{-1}$. The exact route of metabolization of pindolol in man is not yet known.

The calculation of the invasion constant k_1 always involves some problems if the absorption is rapid and if only a limited number of determinations in the invasion period are available. Both of the two methods applied for the calculation of k_1 are imprecise to a certain degree but the validity of the SIGMA-MINUS method can be estimated by determining the correlation coefficient of the calculated regression line which in the case of pindolol was 0.92 or better. In addition, the variation of k_1 is less using the SIGMA-MINUS procedure indicating that this method should be preferable. On the other hand, t_{max} calculated by using k_1 -values of the DILLER method fits better to t_{max} observed in the drawn plasma curves of the individual subjects. So both methods seem to be applicable in this study with certain restrictions.

The volume of distribution of pindolol was 136 and 142 l, respectively, which is in congruence with the values obtained with propranolol and practolol (SHAND et al., 1970; BODEM and CHIDSEY, 1973), indicating similar distribution patterns of these compounds closely related concerning chemical structure, partition coefficient, and pk_a -values.

Summary. The absorption, distribution, and excretion kinetics of pindolol have been investigated in 17 volunteers after an oral dose or an intravenous infusion of 5 mg of the drug. The time course of the plasma levels seemed to follow first order kinetics with an apparent half life of 3.6 (oral) and 3.1 (i.v.) hours. The cumulative urinary excretion at $t = \infty$ was found to be 36.1% and 39.2% of the dose administered indicating an extensive metabolization of the drug. The absorption rate was calculated to be 92%. The distribution volume was 136 l. Mean peak plasma levels were registered 80 min after the oral administration exhibiting a 4-fold variation after identical doses. The renal clearance was $216 \text{ ml} \times \text{min}^{-1}$, total clearance was $483 \text{ ml} \times \text{min}^{-1}$. The amount of protein bound pindolol in plasma was 57%.

Key words: Pindolol, beta-blockade, pharmacokinetics, man.

Subject	H o u r s									
	0.5	1	2	3	4	6	8	12	24	
I	2.4	10.8	17.6	19.4	16.6	9.2	10.0	4.8	--	
II	9.8	21.8	32.0	26.8	18.2	12.0	5.2	4.0	--	
V	44.5	43.3	51.3	44.5	32.0	25.0	20.0	9.0	--	
VIII	31.0	81.4	56.2	55.2	52.4	45.0	26.2	17.5	0.55	
IX	7.3	16.9	32.0	25.4	22.0	14.1	9.3	4.52	0.28	
X	5.9	21.8	24.6	22.6	18.5	12.6	7.2	2.82	2.05	
XII	18.9	28.8	22.2	20.0	14.0	8.5	7.0	4.4	0.26	
XV	5.0	29.4	26.9	17.5	13.3	6.9	3.8	3.4	1.25	
XVI	31.7	38.1	38.5	32.1	30.2	24.5	16.6	10.5	0.76	
XIX	18.1	26.3	25.8	23.3	21.35	15.9	10.6	5.3	0.99	
XXI	9.9	25.7	19.7	16.1	13.2	5.4	2.4	0.6	--	
XXIV	67.4	44.6	36.0	28.7	23.0	16.0	10.7	6.7	0.33	
$\bar{x}$	21.01	33.08	31.9	27.6	22.89	16.26	10.75	6.12	0.81	
S	19.53	18.16	12.0	11.59	11.1	10.96	6.98	4.46	0.61	
$S_{\bar{x}}$	5.63	5.24	3.47	3.34	3.2	3.17	2.01	1.28	0.22	

Table 1 - Plasma concentrations after oral administration of 5 mg of pindolol.

Subject	H o u r s												
	-2.75	-1.5	-0.25	0	0.25	0.5	1	2	3	4	6	8	12
A	8.8	11.7	13.9	14.2	13.4	12.9	12.1	11.4	8.0	6.5	4.5	3.9	1.5
B	4.5	13.5	14.7	17.3	15.7	16.0	13.6	10.6	8.3	6.7	3.8	1.6	-
C	5.9	15.2	24.3	27.5	21.3	19.5	16.1	12.0	9.3	7.5	5.3	4.5	3.4
D	13.5	39.5	55.9	54.9	50.0	43.9	36.5	25.9	23.2	14.1	6.5	3.8	1.1
E	4.0	34.4	36.8	38.4	38.4	33.8	29.4	24.8	12.8	11.2	5.5	2.4	0.8
$\bar{x}$	7.0	22.9	16.4	30.5	27.8	25.2	21.5	16.9	12.3	9.2	5.1	3.2	1.7
$S_{\bar{x}}$	2.2	5.2	9.7	8.3	7.1	5.4	4.9	3.4	2.9	1.5	0.5	0.5	0.6

Table 2 - Plasma level during and after intravenous infusion of pindolol (dose, see Table 4)

Subject	a (ng/ml)	k_1^* (h^{-1})	Inv.- $t_{0.5}$ (h)	t_{max}^* (h)	k_2 (h^{-1})	El.- $t_{0.5}$ (h)	F_0^* ($\mu g \cdot h \cdot ml^{-1}$)	E_{cum} (%)	V (l)	Cl_{tot} ($ml \cdot min^{-1}$)	Cl_{ren} ($ml \cdot min^{-1}$)
I	23.9	0.898	0.77	2.40	0.148	4.66	161.6	25.3	227	515.5	153.4
II	40.0	1.668	0.42	1.39	0.224	3.10	178.8	27.3	135	466.7	144.0
V	64.1	1.910	0.36	1.39	0.169	4.10	379.6	--	85	219.7	--
VIII	116.2	6.800	0.10	0.53	0.210	3.31	533.9	59.3	47	150.5	77.3
IX	41.3	1.112	0.62	1.85	0.214	3.23	193.0	41.1	131	431.6	198.9
X	35.7	1.285	0.54	1.65	0.224	3.10	159.3	66.6	152	522.7	317.4
XII	32.4	3.920	0.18	0.80	0.198	3.49	163.2	25.3	168	511.5	160.3
XV	20.1	1.088	0.64	2.14	0.138	5.04	145.6	29.1	270	572.7	197.4
XVI	60.0	3.161	0.22	0.97	0.177	3.91	339.5	28.0	90	244.9	73.4
XIX	33.3	1.675	0.41	1.57	0.152	4.56	218.9	34.9	163	380.0	154.9
XXI	36.9	2.545	0.27	0.96	0.352	1.97	100.5	22.6	147	792.0	190.4
XXIV	57.5	--	--	--	0.208	3.34	276.1	38.1	95	301.6	128.0
$\bar{x}$	46.8	2.360	0.41	1.42	0.200	3.65	239.2	36.1	142	425.8	163.2
$S_{\bar{x}}$	7.5	0.520	0.06	0.17	0.010	0.24	37.2	4.4	17	51.5	20.0

* According to Dillier

Table 3 - Pharmacokinetic parameters after oral administration of 5 mg of pindolol.

a = initial concentration; k_1 = invasion rate constant; $Inv \cdot t_{0.5}$ = invasion half life time; t_{max} = time of maximum plasma concentration; k_2 = elimination rate constant; $El \cdot t_{0.5}$ = elimination half life time; F_0^* = total area below the serum curve; E_{cum} = cumulative urinary excretion; V = volume of distribution; Cl_{tot} = total clearance; Cl_{ren} = renal clearance.

Subject	Dose (mg)	C_0 (ng/ml)	k_2 (h^{-1})	$t_{0.5}$ (n)	F_0^{∞} ($\mu g \cdot h \cdot ml^{-1}$)	E_{cum} (%)	V (l)	Cl_{tot} ($ml \cdot min^{-1}$)	Cl_{ren} ($ml \cdot min^{-1}$)
A	4.26	22.6	0.150	4.42	150.8	37.7	210	525.0	176.3
B	4.71	29.7	0.281	2.46	105.6	40.1	160	749.3	282.7
C	4.71	25.3	0.153	4.53	165.5	79.9	190	484.5	371.5
D	4.83	59.6	0.326	2.13	282.8	37.6	50	271.7	106.5
E	4.72	68.7	0.331	2.10	207.5	41.3	70	386.2	143.2
$\bar{x}$	4.65	41.2	0.248	3.13	179.8	39.2	136	483.3	216.1
$S_{\bar{x}}$	0.10	9.6	0.040	0.55	30.7	0.9	32.2	79.6	48.3

Table 4 - Pharmacokinetic parameters after intravenous administration of pindolol.

C_0 = initial concentration; k_2 = elimination rate constant; $t_{0.5}$ = elimination half life time; F_0^{∞} = total area below the serum curve; E_{cum} = cumulative urinary excretion; V = volume of distribution; Cl_{tot} = total clearance; Cl_{ren} = renal clearance.

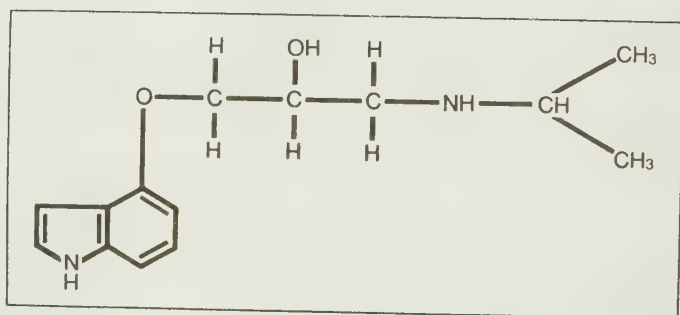


Fig. 1 : Structural formula of pindolol



Fig. 2 : Plasma level time course ($\bar{x} \pm S_{\bar{x}}$) after the oral administration of 5 mg of pindolol



Fig. 3 : Plasma level time course ($\bar{x} \pm S_{\bar{x}}$) during and after the intravenous administration of 5 mg of pindolol

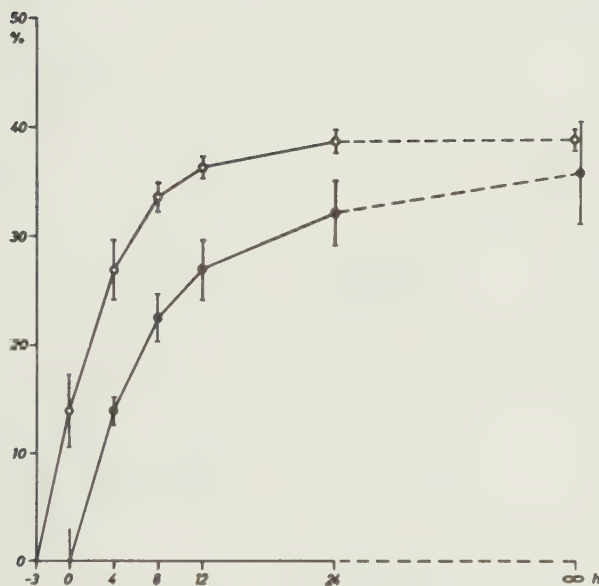


Fig. 4 : Cumulative urinary excretion of pindolol after oral administration (●—●) and intravenous infusion (○—○) of 5 mg of pindolol

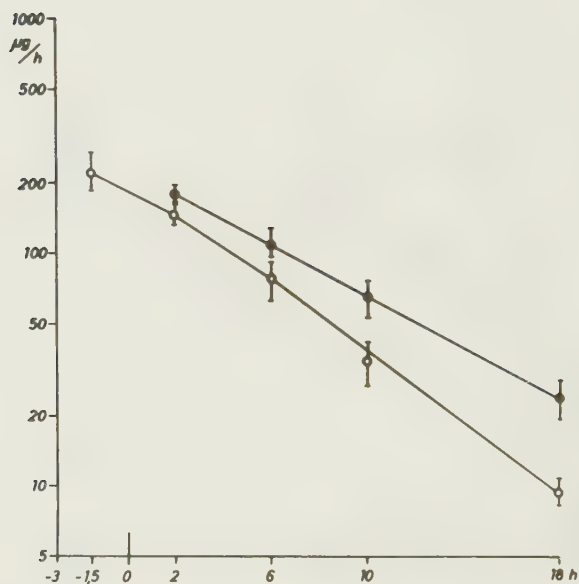


Fig. 5 : Urinary excretion rates for orally (●—●) and intravenously (○—○) administered pindolol

References

1. ABLAD, B. M. ERVIK, J. HALLGREN, G. JOHNSON, L. SÖLVELL : Pharmacological Effects and Serum Levels of Orally Administered Alprenolol in Man. Eur.J.Clin.Pharmacol. 5, 44-52 (1972)
2. BARRETT, A.M., J. CARTER : Comparative chronotropic activity of β -adrenoceptive antagonists. Brit.J.Pharmacol. 40, 373 (1970)
3. BODEM, G., C.A. CHIDSEY : Pharmacokinetics of Practolol in Man. J.Clin.Pharmacol.Ther. - in press
4. BRODIE, B.B., W.W. REID : The value of determining the plasma concentration of drugs in animals and man. Fundamentals of Drug Metabolism and Drug Disposition. Edited by B.N. LaDu, H.G. Mandel, E.L. Way. Baltimore, Williams and Wilkins Company, 328-339 (1971)
5. DENGLE, H.J., M. EICHEL-BAUM, H. HENGSTMAN, J. WIEBER : Pharmacokinetic Studies in Man with Sparteine. Pharmacol.Clin. 2, 189-195 (1970)
6. DENGLE, H.J., G. BODEM, K. WIRTH : Pharmakokinetische Untersuchungen mit H^3 -Digoxin und H^3 -Lanatosid beim Menschen. Arzneimittel-Forsch. 23, 64-74 (1973)
7. DILLER, W. in : P. Bünger, W. Diller, J. Führ. Arzneimittel-Forsch. 11, 247 (1961)
8. FITZGERALD, J.D., B. SCALES : Effect of a new Adrenergic Beta-Blocking Agent (ICI 50, 172) on Heart Rate in Relation to its Blood Levels. Int.J.clin.Pharmacol. 1, 6, 467-474 (1968)
9. GEORGE, C.F., T. FENYVESI, M.E. CONOLLY, C.T. DOLLERY : Pharmacokinetics of Dextro-, Laevo-, and Racemic Propranolol in Man. Eur.J.Clin.Pharmacol. 4, 74-76 (1972)
10. GIBALDI, M., R. NAGASHIMA, G. LEVY : Relationship between drug concentration in plasma or serum and amount of drug in the body. J.Pharm.Sci. 58, 193-197 (1969)
11. GIUDICELLI, J., H.SCHMITT, J. BOISSIER : Studies on DL-4-(2-hydroxy-3-isopropyl-aminopropoxy)-indole, a new potent beta adrenergic blocking drug. J.Pharmacol.Exp.Ther. 168, 345 (1969)
12. GUGLER, R., W. HÜBEL, G. BODEM, H.J. DENGLE : Relationship between β -adrenergic blockade and plasma level of pindolol in man. - in preparation -

13. HICKS, D.C., A.G. ARBAB, P. TURNER, M. HILLS : A comparison of intravenous pindolol and propranolol in normal man. J.clin.Pharmacol. 12, 212-216 (1972)
14. HILL, R.C., P. TURNER : The effect of a new beta-adreno-ceptive receptor blocking drug on heart rate in man. Brit.J.Pharmacol. 32, 663 (1967)
15. HILL, R.C., P. TURNER : Preliminary investigations of a new beta-adrenoceptive receptor blocking drug, LB 46, in man. Brit.J.Pharmacol. 36, 368 (1969)
16. JOHNSON, G., J. SJÖGREN, L. SÖLVELL : Beta-Blocking Effect and Serum Levels of Alprenolol in Man after Administration of Ordinary and Sustained Release Tablets. Eur.J.Clin.Pharmacol. 3, 74-81 (1971)
17. KOCH-WESER, J. : Serum Drug Concentrations as Therapeutic Guides. New England J.of Medicine, 287, 227-231 (1972)
18. KRIEGLSTEIN, J., G. KUSCHINSKY : Quantitative Bestimmungen der Eiweißbindung von Pharmaka durch Gel-filtration. Arzneimittel-Forsch. 18, 287-289 (1968)
19. LEVY, J.V. : Cardiovascular Effects of Prinodolol (LB 46), a Potent Beta-Adrenergic Receptor Antagonist. J.Clin.Pharmacol. 11, 249-260 (1971)
20. LUBAWSKI, J., J. WALE : Studies with LB 46, a new β -receptor blocking drug. Europ.J.Pharmacol. 6, 345 (1969)
22. NOESCH, E. : Proof of the general validity of Dost's law of corresponding areas Eur.J.Clin.Pharmacol. - in press
23. OLSSON, B.S., E. VARNAUSKAS : Duration of beta-receptor blockade after oral administration of LB-46. Eur.J.Clin.Pharmacol. - in press
24. PACHA, W.L. : A method for the fluorometric determination of 4-(2-Hydroxy-3-isopropyl-aminopropoxy)-indole, a β -blocking agent, in Plasma and Urine. Experientia 25, 802-803 (1969)
21. MARTIN, B.K. : Drug urinary excretion data - some aspects concerning the interpretation. Brit.J.Pharmac.Chemother. 29, 181-190 (1967)

25. PATERSON, J.W., : The pharmacodynamics and metabolism
M.E. CONOLLY, C.T. DOLLERY, of propranolol in man.
A. HAYES, R.G. COOPER Pharmacol. Clin. 2, 127-133 (1970)
26. SAAMELI, K. : Comparative studies with β -receptor
blocking agents and quinidine.
Helv.Physiol.Acta 25, CR 432 (1967)
27. SHAND, D.G., : Plasma Propranolol Levels in Adults.
E.M. NUCKOLLS, J.A. OATES With Observations in four Children.
Clin.Pharmacol.Ther. 11, 112-120,
(1970)
28. WAGNER, J.G. : Pharmacokinetics.
J.M. Richards Laboratory, Grosse
Pointe Park, Michigan, 5-10 (1969)

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